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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,379	BAKALETZ ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-62* is/are pending in the application.

4a) Of the above claim(s) *49-60 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-48 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/20/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence report (2)*.

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicants' preliminary amendments filed 09/07/04 and 04/05/05. With this, Applicants have amended the specification and drawing(s).

Election

2) Acknowledgment is made of Applicants' election filed 01/17/05 in response to the lack of unity mailed 12/09/04. Applicants have elected invention I, claims 32-48, with traverse. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)). Applicants note the inadvertent omission of claims 61 and 62 from the restriction requirement. The Office regrets this inadvertent omission. Claim 61 is now placed in invention I and has been examined along with the elected claims 32-38. Claim 62, drawn to a kit comprising an antibody, is placed in invention III.

Status of Claims

3) Claims 1-31 have been canceled via the amendment filed 12/11/00.

Claims 32-62 have been added via the amendment filed 12/11/00.

Claims 32-62 are pending.

Claims 49-62 are withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 32-48 and 61 have been elected and are under examination. A First Action on the Merits on these claims is issued.

Sequence Listing

4) Acknowledgment is made of Applicants' submission of the raw sequence listing and the CRF which have been entered on 12/11/02.

Information Disclosure Statement

5) Acknowledgment is made of Applicants' information disclosure statement filed 02/20/01. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

6) The instant application is a continuation of the PCT application, PCT/US99/11980, filed 05/28/99, which claims foreign priority to application 9812613.9, filed 06/11/1998 in the United Kingdom.

It is noted that Applicants have submitted a certified copy of the priority document on 12/11/00.

Specification - Informality

7) The specification is objected to for the following reason(s):

The use of the trademark in the instant specification has been noted. For example, see page 24, line 3: 'Amplitaq'; page 38, line 30 and page 39, lines 5, 6 and 15: page 39, line 12: 'Sephacryl S-500'; page 39, line 2: 'Qiagen'; page 39, line 14: 'Filton Omega'. The recitation should be capitalized wherever it appears and be accompanied by the generic terminology. Each letter of the trademark must be capitalized. See M.P.E.P 608.01(V) and Appendix 1. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar correction to the trademark, wherever it appears.

Rejection(s) under 35 U.S.C § 101

8) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

9) Claims 32-36 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Instant claims, as written, do not sufficiently distinguish over peptides as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed product(s) and the naturally occurring product(s). In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980)*. The claim(s) should be amended to indicate the hand of the inventor, e.g., by insertion of the limitation 'A purified' as described in the paragraph

bridging pages 14 and 15 of the instant specification. See MPEP 2105.

Double Patenting

10) The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

11) Claims 32, 37 and 46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5 of Bakaletz *et al.* (US 5,843,464 – Applicants' IDS) ('464) and claims 1, 2, 8 and 9 of Bakaletz *et al.* (US 6,436,405) ('405) respectively. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See e.g., *In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998)*; *In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993)*; *In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir, 1985)*. Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 1, 2 and 5 of Bakaletz *et al.* ('464) and claims 1, 2, 8 and 9 of Bakaletz *et al.* ('405) fall within the scope of instant claims 32, 37 and 36 respectively. In other words, instant claims 32, 37 and 46 are anticipated by claims 1, 2 and 5 of Bakaletz *et al.* ('464) and claims 1, 2, 8 and 9 of Bakaletz *et al.* ('405). Bakaletz's peptide and synthetic peptide comprises SEQ ID NO: 1, RSDYKFYEDANGTRDHKK, which has 88.6% sequence identity with the instantly recited

SEQ ID NO: 1 and therefore qualifies as an 'antigenically related variant' of SEQ ID NO: 1 having at least 75% identity thereto. See the attached sequence alignment report. The structure of the prior art peptide of SEQ ID NO: 1 indicates that it does not include SEQ ID NO: 5 or SEQ ID NO: 6.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Written Description)

12) Claims 32, 37-40, 46-48, 61 and 62 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the peptide 'variants' having at least 75% identity recited in the instant claims does not exist independent of its function, i.e., ability to serve as a vaccine and a diagnostic reagent, ability to prevent *Haemophilus influenzae* infection, and capacity to immunologically mimick the corresponding antigenic determinant site of the P5-like fimbrin protein of non-typeable *Haemophilus influenzae*. The specification discloses diagnostic applications or screening intentions and prophylactic or vaccine applications for the 75% identical peptide variants. However, the instant specification fails to teach a single variant peptide sequence having 75% identity to the amino acid sequence of SEQ ID NO: 1, 2, 3 or 4 and concurrently having the above-identified biologic functions. Diagnostic or screening applications and vaccine or prophylactic applications minimally require a specific interaction with a binding or neutralizing compound. The precise structure or relevant identifying characteristics of DNA molecules that encode variant peptides having 75% identity to the amino acid sequence of SEQ ID NO: 1, 2, 3 or 4 and the above-identified functional activities can only be determined empirically by actually making DNA molecules that encode the peptides of the recited variability, i.e., the instantly recited 75% sequence identity, and testing the varied DNA molecules to determine whether they encode the 75% modified peptide variants having the particularly disclosed biologic activities. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention or the method includes the use of a peptide variant having at least 75% identity to the amino acid sequence of SEQ ID NO: 1, 2, 3 or 4 is insufficient to meet the

adequate written description requirement of the claimed invention. The peptide of SEQ ID NO: 1, 2, 3 or 4 has specific biologic properties dictated by the structure of the peptide and the corresponding structure of the structural gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the peptide encoded, and the function of the encoded peptide. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the at least 75% modified peptide variants. Applicants have not shown that variation or modification of a reference sequence encoding a reference peptide as claimed would automatically predict the production of a peptide having the recited functional activities. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of DNA molecules encoding a representative number of species of peptide variants of at least 75% sequence identity as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of a peptide of SEQ ID NO: 1, 2, 3 or 4, a skilled artisan cannot envision the detailed chemical structure of all the peptide variant species encompassed by the recited molecule. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that its is a part of the invention and a reference to a potential method of isolating it. The peptide variants themselves are required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

13) Claims 32, 37-40, 46-48, 61 and 62 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a peptide comprising the amino acid sequence of SEQ ID NO: 1, 2, 3 or 4; a chimeric polypeptide comprising the same; and a composition comprising the same which induces an immune response against nontypeable *Haemophilus influenzae* in a mammal on administration to a mammal in a method of inducing an immune response to nontypeable *Haemophilus influenzae*, and a reagent kit comprising the same, does not reasonably provide enablement for 'peptide variants' of SEQ ID NO: 1, 2, 3, or 4 having an identity of at least 75% while having the capability to 'immunologically mimick the corresponding antigenic determinant site of the P5-like fimbrin protein of non-typeable *Haemophilus influenzae'*, the ability

to induce an immune response to *Haemophilus influenzae* infection in a method of inducing said immune response, ability to serve as a vaccine and a diagnostic reagent, and ability to prevent *Haemophilus influenzae* infection in a method of said prevention, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant application, the nature of the invention is related to peptide variants having at least 75% identity to a reference peptide sequence and the capacity to serve as a vaccine in a method of 'preventing' *H. influenzae* infection, or inducing an immune response to *H. influenzae* in a susceptible mammal; the capacity to serve as diagnostic reagent; and the capacity to immunologically mimick the 'corresponding antigenic determinant site of the P5-like fimbrin protein of non-typeable *Haemophilus influenzae*'. The at least 75% identical peptide 'variant' product used in the vaccine composition, diagnostic kit, and the two claimed methods is *required* to have the biologic capabilities identified above. However, the instant specification does not teach how to make peptide 'variants' of the amino acid sequence of SEQ ID NO: 1, 2, 3 or 4 with 25% of its amino acids varied or modified in such a way that the resultant peptide variants still maintain the prophylactic and diagnostic activities. Neither the specification nor the art discloses a peptide variants that are at least 25% non-identical to the amino acid sequence of SEQ ID NO: 1, 2, 3 or 4 which variants retain the above-identified biologic functions. The instant specification fails to demonstrate that peptide variants having at least 75% identity to SEQ ID NO: 1, 2, 3 or 4, if prepared by one of skill in the art, would retain all the functional or biological properties of the native peptide of SEQ ID NO: 1, 2, 3 or 4. It should be noted that predictability or unpredictability

is one of the *Wands* factors for enablement. The precise structural composition of the claimed peptide variants is not disclosed, without which one of ordinary skill in the art cannot make and use the claimed product in the claimed method without undue experimentation. The specification lacks disclosure as to how to produce peptide variants having at least 75% sequence identity to SEQ ID NO: 1, 2, 3 or 4 and at the same time having all the necessary functions for use as a vaccine and a diagnostic reagent. There is no predictability that such peptide variants having as much as 25% dissimilarity with the peptide of SEQ ID NO: 1, 2, 3 or 4 would remain functional as an effective vaccine or diagnostic reagent. This is critical because the art reflects sensitivity of proteins or polypeptides to alteration of even a single amino acid residue in its amino acid sequence. An alteration in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar *et al* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) provided similar teachings and showed that in the protein, transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. In the instant case, it is unlikely that a peptide molecule having as much as 25% dissimilarity with the native peptide of SEQ ID NO: 1, 2, 3 or 4 as recited, would have its primary, secondary or tertiary structure unchanged and would have all the biologic activities retained. The effects of such a high dissimilarity upon the peptide structure and function are unpredictable. One of skill in the art cannot predict that such a peptide variant would have its immunologic or biologic specificity (i.e., *H. influenzae*-specificity) retained. Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al* also taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid

substitutions can be made with a reasonable expectation of maintaining function(s) is limited. Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a peptide, with as much as 25% dissimilarity to the peptide of SEQ ID NO: 1, 2, 3 or 4, the prophylactic and diagnostic activities of the claimed peptide variants could not be predicted, based solely on the sequence identity, nor would it be expected to be the same as that of the peptide of SEQ ID NO: 1, 2, 3 or 4. For example, if one nucleotide in the nucleotide sequence that encodes the peptide of SEQ ID NO: 1, 2, 3 or 4 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the peptide expressed will have little in common structurally or functionally with the native peptide of SEQ ID NO: 1, 2, 3 or 4. There is no certainty that amino acid substitutions at any position would yield a peptide that retains the function and/or the specificity of the native peptide of SEQ ID NO: 1, 2, 3 or 4. The specification fails to demonstrate that a peptide having 25% structural dissimilarity to SEQ ID NO: 1, 2, 3 or 4 would be functionally equivalent to the native peptide of SEQ ID NO: 1, 2, 3 or 4 particularly with regard to the prophylactic and diagnostic activities. One simply cannot predict what effects a given deletion, insertion or modification in the amino acid sequence would cause, and therefore such modified molecules are not enabled as Applicants' invention. Applicants have not enabled the full scope of the invention as claimed for those peptide molecules which are altered or varied. The specification only discloses peptide of SEQ ID NO: 1, 2, 3 or 4. Undisclosed and unidentified functional peptide molecules of at least 25% non-identity encompassed in the claims are not enabled for their scope. Although a skilled artisan might envision making a number of changes in the reference polynucleotide sequence in accordance with Applicants' disclosure, it is highly uncertain that the peptide variants as recited would be functionally equivalent to the native peptide of SEQ ID NO: 1, 2, 3 or 4. The altered peptides would vary in an unknown or unpredictable manner from the disclosed native peptide sequence. For these reasons, making and using of the instantly claimed peptide variants having the desired function(s) is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of

ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as recognized in the state of the art, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

14) Claim 48 is rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of immunizing chinchillas comprising administering to said chinchillas with 10 micrograms of PD, LPD-LB1(f)$_{2,1,3,}$ or LB1(f) peptide fused to a T-cell promiscuous epitope from measles virus fusion protein wherein the peptide comprises the specific amino acid sequence of SEQ ID NO: 28, does not reasonably provide enablement for a method of 'preventing' *Haemophilus influenzae* infection comprising administering to said mammal an effective amount of a vaccine composition comprising the peptide of any one of claims 32-36 or the chimeric polypeptide of any one of claims 37-45, as recited currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claim 48 is evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, Example 4a of the specification describes a method of actively immunizing chinchillas comprising administering to said chinchillas with a composition comprising two adjuvants, aluminum phosphate and 3-O-acylated MPL and 10 micrograms of PD, LPD-LB1(f)$_{2,1,3,}$ or LB1(f) peptide fused to a T-cell promiscuous epitope from measles virus fusion protein wherein the peptide comprises the specific amino acid sequence of SEQ ID NO: 28. The antibody titers of the immunized chinchillas were measured and their specific recognition tested

with the P5-like fimbrin protein from three strains of non-typeable *Haemophilus influenzae* (see pages 39 and 40, and Figure 12). Thus, a method of active immunization of chinchillas with a specific composition comprising two adjuvants and the above-identified peptide(s) is enabled. However, outside this scope, the disclosure is not enabling for a method of 'preventing' *Haemophilus influenzae* (typeable or non-typeable) infection comprising administering to a mammal, including a human, an effective amount of a vaccine composition comprising the peptide of any one of claims 32-36 or the chimeric polypeptide of any one of claims 37-45, as claimed currently. The *Webster's II New Riverside University Dictionary* (1984) defines the term 'prevent' as 'to keep from happening'. See page 933. Infection due to typeable and/or non-typeable *H. influenzae* encompasses microbial cell invasion and growth or multiplication of the bacteria therein. The term 'infect' is defined in the illustrated *Stedman's Medical Dictionary* (24th Edition, 1982, page 707) as 'to enter, invade, inhabit, or to dwell internally'. The specification does not support a method which keeps the process of infection from happening, or a method which prevents the entry and invasion of typeable and/or non-typeable *H. influenzae* into a cell or its internal dwelling on administration of the peptide of any one of claims 32-36 or the chimeric polypeptide of any one of claims 37-45 to a mammal, human or non-human. What constitutes an 'effective amount of a vaccine according to claim 46' is not taught. Furthermore, there is absolutely no showing that 'any antigenically related variants' of SEQ ID NO: 1, 2, 3 or 4 'which have an identity of at least 75%' as recited in claim 32 would have the ability to 'prevent' infection due to typeable and/or non-typeable *H. influenzae* in a mammal. Therefore, while a method of actively immunizing chinchillas with the one of the recited peptides or polypeptides is enabled comprising administering to said chinchillas with a composition comprising two adjuvants, aluminum phosphate and 3-O-acylated MPL and 10 micrograms of PD, LPD-LB1(f)$_{2,1,3,}$ or LB1(f) peptide fused to a T-cell promiscuous epitope from measles virus fusion protein wherein the peptide comprises the specific amino acid sequence of SEQ ID NO: 28, a method of "preventing" typeable and/or non-typeable *Haemophilus influenzae* infection in a mammal, including a human, is not. The full scope of the claims is not commensurate with the enabling disclosure. Furthermore, it should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. The 'prevention' of a bacterial disease with a peptide composition is not a predictable event, absent a concrete showing. Due to the lack of specific disclosure and/or guidance, the lack of working examples enabling the full scope, the

breadth of the instant claims, the unpredictability factor, and the quantity of experimentation necessary, undue experimentation would have been required at the time of the effective filing date of the instant application for one of ordinary skill in the art to reproducibly practice the full scope of the claimed method of 'preventing *Haemophilus influenzae* infection' in a mammal, including a human. The ability to reproducibly practice the full scope of the claimed method is well outside the realm of routine experimentation. The specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. The enablement (scope) provisions of 35 U.S.C. § 112, first paragraph, are not met.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

15) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

16) Claims 32-48 and 61 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 32 is vague and indefinite in the limitation: 'antigenically related variants of said sequences which have an identity of at least 75% and are capable of immunologically mimicking the corresponding antigenic determinant site of the P5-like fimbrin protein', because it is unclear what is meant by 'an identity of at least 75%'. Whether or not this represents structural identity or functional/biological identity, contiguous or discontiguous sequence identity is unclear. Furthermore, what constitutes 'the corresponding antigenic determinant site of the P5-like fimbrin protein' is not clear. What is encompassed in the limitations: 'those peptides provided in SEQ ID NO: 5 or SEQ ID NO: 6' is not clear. Are the peptides excluded via the proviso language peptides of any size within SEQ ID NO: 5 or SEQ ID NO: 6, or are these peptides consisting of SEQ ID NO: 5 or SEQ ID NO: 6?

(b) Claim 45 is indefinite in the recitation: 'the amino acid sequence of the polypeptide is provided in Figure 5', because it fails to point out what is included or excluded by the claim language, especially because Figure 5 is subject to changes via amendments, which would change the scope of the claim. According to M.P.E.P 2173.05(s), where possible, claims are to be complete in themselves. Incorporation by reference to Tables, and Figures, or Examples is a necessity

doctrine, not for Applicants' convenience. See *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993). In order to obviate the rejection, it is recommended that Applicants recite the exact polypeptide or protein by referring to its SEQ ID number, instead of referring to it via a Figure.

(c) Claims 47 and 48 are vague and indefinite in the recitation 'effective amount' because it is a relative term. The term 'effective' is not specifically defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the claims. What amount qualifies as an 'effective' amount, and in what capacity the amount is 'effective', i.e., prophylactically effective, therapeutically effective etc., is unclear.

(d) Claim 48 lacks proper antecedent basis in the limitation: 'a vaccine according to claim 46'. For proper antecedence, it is suggested that Applicants replace the limitation with --the vaccine according to claim 46--.

(e) Claim 46 lacks proper antecedent basis in the limitation: 'at least one peptide or polypeptide from claim.....'. For proper antecedence, it is suggested that Applicants replace the limitation with --at least one of said peptide or polypeptide from claim....--.

(f) Claim 44 has improper antecedent basis in the limitation: 'the peptide components'. Claim 44 depends from claim 42, which does not include the limitation: 'components'.

(g) Claim 44 lacks antecedent basis in the limitations: 'lipoprotein D .... SEQ ID NO: 2 .... SEQ ID NO: 5 ..... SEQ ID NO: 3'. Claim 44 depends from claim 42 which already recites 'lipoprotein D', 'SEQ ID NO: 2', SEQ ID NO: 5' and 'SEQ ID NO: 3'.

(h) Claim 61 is vague, indefinite, incorrect and/or confusing in the limitation: 'a LB1(f) peptide of claims 32-36'. None of claims 32-36 include the limitation 'a LB1(f) peptide'.

(i) Claims 33-36 are vague and confusing in the limitation: 'the amino-acid sequence provided in SEQ ID NO: ...'. What is encompassed in the limitation: 'provided in SEQ ID NO: ...' is not clear. Via this language, whether or not Applicants intend to cover the full-length sequence or partial sequence(s) within the recited SEQ ID NO is not clear. Whether or not the limitation 'provided in' encompasses closed or open claim language is unclear. Clarification/correction is requested.

(j) Analogous criticism applies to claim 42 with regard to the limitation: 'provided in

SEQ ID NO: ..'.

(k) Claim 47 is indefinite in the limitation: 'inducing an immune response ... to *Haemophilus influenzae* infection comprising the administration .... the vaccine according to claim 46'. Claim 46 depends from claim 32, which recites that the peptide is from 'non-typeable' *Haemophilus influenzae.* It is unclear how a peptide is from 'non-typeable' *Haemophilus influenzae* can induce an immune response to the broad genus of '*Haemophilus influenzae*'.

(l) Analogous criticism applies to claim 48 with regard to the limitation: 'preventing *Haemophilus influenzae* infection'.

(m) Claims 33-41, 43-48 and 61, which depend directly or indirectly from claim 32 and 42, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

17) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in-
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

18) Claims 32, 37 and 46-48 are rejected under 35 U.S.C. § 102(e)(2) as being anticipated by Bakaletz *et al.* (US 5,843,464, filed 06/02/1995 – Applicants' IDS).

Bakaletz *et al.* ('464) taught a synthetic chimeric fimbrin peptide LB1 which comprises a peptide comprising the amino acid sequence of SEQ ID NO: 1 having the structure: RSDYKFYEDANGTRDHKK. The synthetic peptide is a fimbrin subunit. See claim 1; last paragraph in column 3; and lines 39-39 in column 4. This peptide sequence has 88.6% sequence identity with the instantly recited SEQ ID NO: 1 and therefore qualifies as an 'antigenically related variant' of SEQ ID NO: 1 having at least 75% identity thereto. See the attached sequence alignment report. The structure of the prior art peptide of SEQ ID NO: 1 indicates that it does not include SEQ ID NO: 5 or SEQ ID NO: 6. A synthetic chimeric peptide comprising SEQ ID NO: 1 and a second peptide unit comprising a T cell epitope is taught (see claim 2; first paragraph in column 4; and lines 39-49 in column 4). An immunogenic composition comprising the synthetic

chimeric peptide and a pharmaceutically acceptable carrier is taught (see claim 5). Bakaletz *et al.* ('464) further taught a method of inducing immune response in chinchillas (i.e., a mammal susceptible to *Haemophilus influenzae* infection) comprising administering to chinchillas a preparation comprising the synthetic chimeric fimbrin pepide LB1 contained in an adjuvant (i.e., a vaccine composition) which method inhibits nasopharyngeal colonization of non-typeable *Haemophilus influenzae*. See column 8; and lines 1-6 of column 9. The synthetic chimeric peptide is administered to prevent otitis media due to non-typeable *Haemophilus influenzae* (see lines 30-36 in column 10) and it inhibits adherence of non-typeable *Haemophilus influenzae* to host tracheal epithelium (see lines 1-22 in column 8). Therefore, the prior art method of inducing immune response in chinchillas by administering to chinchillas a preparation comprising the synthetic chimeric fimbrin pepide LB1 contained in an adjuvant inherently serves as a method of preventing *Haemophilus influenzae*.

Claims 32, 37 and 46-48 are anticipated by Bakaletz *et al.*

Rejection(s) under 35 U.S.C § 103

19) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth In section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth In *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

20) Claims 38 and 39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bakaletz *et al.* (US 5,843,464, filed 06/02/1995 – Applicants' IDS) as applied to claim 32 and 37 above, and further in view of Dunn *et al.* (6,248,562, filed 04/29/1994).

The reference of Dunn *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Bakaletz *et al.* ('464) are explained above, which do not expressly teach the presence of a purification tag peptide sequence in their chimeric polypeptide.

However, the use of a purification tag peptide sequence such as a histidine tag sequence in a chimeric polypeptide for the purpose of facilitating easy purification was well known and commonly practice in the art at the time of the invention. For instance, Dunn *et al.* taught that chimetic proteins can be designed to end in an affinity tag, such as, His-tag, for the purpose of facilitating easy purification. See lines 21-23 in column 7.

Given that it is routine to use a His-tag in a chimeric polypeptide, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include Dunn's histidine affinity tag in to Bakaletz's ('464) chimeric polypeptide to produce the instant invention, with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of facilitating the purification of Bakaletz's ('464) chimeric polypeptide as taught by Dunn *et al.*

Claims 38 and 39 are *prima facie* obvious over the prior art of record.

21) Claim 61 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Bakaletz *et al.* (US 5,843,464, filed 06/02/1995 – Applicants' IDS) as applied to claim 32 above.

The teachings of Bakaletz *et al.* ('464) are explained above, which do not expressly teach a reagent kit comprising their synthetic peptide. However, Bakaletz *et al.* ('464) specifically taught that their synthetic chimeric fimbrin peptides can be used as a diagnostic tool in laboratory assays for detecting antibodies to non-typeable *Haemophilus influenzae*. See lines 8-12 in column 9; Table IV; and lines 22-24 in column 10.

Given Bakaletz's express showing that the prior art synthetic chimeric fimbrin peptides are usable as a diagnostic tool in laboratory assays for detecting antibodies to non-typeable *Haemophilus influenzae,* it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to

However, methods of assembling a diagnostic reagent kit using an art-disclosed product was well known and routinely practiced in the art at the time of the invention. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the

time the invention was made to produce such a diagnostic reagent kit for the laboratory diagnosis of non-typeable *Haemophilus influenzae* infections using the synthetic chimeric fimbrin peptides of Bakaletz *et al.* A skilled artisan would have been motivated to produce the instant invention for the expected benefit of making readily available Bakaletz's synthetic chimeric fimbrin peptides, or for commercializing Bakaletz's synthetic chimeric fimbrin peptides for diagnostic use, since Bakaletz *et al.* explicitly teach the use of their peptides as diagnostic tools.

Claim 61 is *prima facie* obvious over the prior art of record.

Objection(s)

22) Claims 32-36, 46 and 61 are objected to for the following reasons:

(a) Claims 32-36 are objected to for the recitation: 'amino-acid sequence'. To be consistent with the practice in the art and with the limitation used in claims 41 and 42, it is suggested that Applicants replace the limitation with --amino acid sequence--.

(b) Claims 46 and 61 are improperly dependent. Any dependent claim which refers to more than one other claim ('multiple dependent claim') shall refer to such other claims in the alternative only.

Remarks

23) Claims 32-48 stand rejected.

24) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (703) 872-9306.

25) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

26) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

June, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER

SEQ ID NO. 1.


```
RESULT 6
US-08-460-502-1
; Sequence 1, Application US/08460502
; Patent No. 5843464
;  GENERAL INFORMATION:
;    APPLICANT:  Bakaletz, Lauren O.
;    APPLICANT:  Kaumaya, Parvin T.
;    TITLE OF INVENTION:  Synthetic Chimeric Fimbrin Peptides
;    NUMBER OF SEQUENCES:  11
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Calfee, Halter and Griswold
;      STREET:  800 Superior Avenue
;      CITY:  Cleveland
;      STATE:  Ohio
;      COUNTRY:  U.S.A.
;      ZIP:  44114-2688
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/460,502
;      FILING DATE:
;      CLASSIFICATION:  424
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Golrick, Mary E.
;      REGISTRATION NUMBER:  34,829
;      REFERENCE/DOCKET NUMBER:  22727/00120
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (216) 622-8458
;      TELEFAX:  (216) 241-0816
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  18 amino acids
;      TYPE:  amino acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-460-502-1

  Query Match           88.6%;  Score 93;  DB 2;  Length 18;
  Best Local Similarity  94.4%;  Pred. No. 1.7e-09;
  Matches   17;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy          1 RSDYKFYEAANGTRDHKK 18
              ||||||||| ||||||||||
Db          1 RSDYKFYEDANGTRDHKK 18


RESULT 7
US-09-148-711A-1
; Sequence 1, Application US/09148711A
; Patent No. 6436405
; GENERAL INFORMATION:
;  APPLICANT:  The Ohio State University
;  TITLE OF INVENTION:  Synthetic Chimeric Fimbrin Peptides
;  FILE REFERENCE:  18525-04010
;  CURRENT APPLICATION NUMBER: US/09/148,711A
;  CURRENT FILING DATE:  1998-09-04
;  PRIOR APPLICATION NUMBER:  08/460,502
;  PRIOR FILING DATE:  1995-06-02
;  NUMBER OF SEQ ID NOS:  12
;  SOFTWARE:  PatentIn version 3.0
; SEQ ID NO 1
;  LENGTH: 18
;  TYPE: PRT
;  ORGANISM: Haemophilus influenza
US-09-148-711A-1

  Query Match           88.6%;  Score 93;  DB 4;  Length 18;
  Best Local Similarity  94.4%;  Pred. No. 1.7e-09;
  Matches   17;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy          1 RSDYKFYEAANGTRDHKK 18
              ||||||||| ||||||||||
Db          1 RSDYKFYEDANGTRDHKK 18
```

SEQ ID NO. 5

RESULT 17
AAW67572
ID AAW67572 standard; peptide; 18 AA.
XX
AC AAW67572;
XX
DT 02-MAR-1999 (first entry)
XX
DE Non-typable H. influenzae fimbrin peptide #1.
XX
KW Chimeric; non-typable Haemophilus influenzae; fimbrin; T-cell epitope;
KW immunogenic composition; immune response.
XX
OS Haemophilus influenzae.
XX
PN US5843464-A.
XX
PD 01-DEC-1998.
XX
PF 02-JUN-1995; 95US-00460502.
XX
PR 02-JUN-1995; 95US-00460502.
XX
PA (OHIS) UNIV OHIO STATE.
XX
PI Kaumaya PTP, Bakaletz LO;
XX
DR WPI; 1999-044514/04.
XX
PT Synthetic chimeric fimbrin peptide - useful for vaccination against non-
PT typable Haemophilus influenzae.
XX
PS Claim 1; Col 3; 16pp; English.
XX
CC The invention relates to the manufacture of a synthetic chimeric peptide
CC comprising a non-typable Haemophilus influenzae fimbrin peptide fused via
CC a linker peptide to a T-cell epitope peptide. The chimeric peptide is
CC used in immunogenic compositions which induce an immune response against
CC non-typable Haemophilus influenzae. This sequence represents an example
CC of a H. influenzae fimbrin peptide used to generate the chimeric peptide
XX
SQ Sequence 18 AA;

  Query Match   94.4%; Score 101; DB 2; Length 18;
  Best Local Similarity 100.0%; Pred. No. 3.2e-09;
  Matches 18; Conservative   0; Mismatches   0; Indels   0; Gaps   0;

Qy   1 RSDYKFYEDANGTRDHKK 18
              ||||||||||||||||||
Db   1 RSDYKFYEDANGTRDHKK 18

RESULT 18
ADA25163
ID ADA25163 standard; peptide; 18 AA.
XX
AC ADA25163;
XX
DT 20-NOV-2003 (first entry)
XX
DE H. influenzae fimbrin subunit peptide #1.
XX
KW fimbrin; non-typable Haemophilus influenzae; NTHi infection;
KW otitis media.
XX
OS Haemophilus influenzae.
XX
PN US6436405-B1.
XX
PD 20-AUG-2002.
XX
PF 04-SEP-1998; 98US-00148711.
XX
PR 02-JUN-1995; 95US-00460502.
XX
PA (OHIS) UNIV OHIO STATE.
XX
PI Bakaletz LO, Kaumaya PTP;
XX
DR WPI; 2003-615247/58.
XX
PT Synthetic chimeric fimbrin peptide, useful for treating Haemophilus
PT influenzae infections.
XX
PS Claim 1; Col 3; 16pp; English.
XX
CC The invention relates to a synthetic chimeric fimbrin peptide. The
CC peptide is useful for treating a non-typable Haemophilus influenzae
CC (NTHi) infection and otitis media. The synthetic peptides do not require
CC tedious purification techniques. The present sequence represents the
CC amino acid sequence of H. influenzae fimbrin subunit peptide #1.
XX
SQ Sequence 18 AA;

  Query Match   94.4%; Score 101; DB 6; Length 18;
  Best Local Similarity 100.0%; Pred. No. 3.2e-09;
  Matches 18; Conservative   0; Mismatches   0; Indels   0; Gaps   0;

Qy   1 RSDYKFYEDANGTRDHKK 18
              ||||||||||||||||||
Db   1 RSDYKFYEDANGTRDHKK 18